Abacavir use and risk of recurrent myocardial infarction: the D: A: D study

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Abstract: OBJECTIVE: To investigate the association between abacavir (ABC) use and recurrent myocardial infarction (MI) among HIV-positive people with a prior MI. DESIGN: International multi-cohort collaboration with follow-up from 1999-2016. METHODS: The rate of recurrent MI was described among D:A:D participants who experienced an index MI whilst in the study, and who remained under follow-up beyond 28 days after this MI. Follow-up was considered to the date of next MI, death, 01/Feb/2016 or 6 months after last clinic visit. Poisson regression models considered associations between recurrent MI and exposure to ABC (use at index MI, current post-MI exposure and cumulative exposure), before and after adjusting for calendar year. RESULTS: The 984 individuals who experienced an index MI during the study (91.3% male, median age 51 at index MI) were followed for 5312 person-years (PY) over which time there were 136 recurrent MIs (rate 2.56/100 PY, 95% Confidence Interval 2.13-2.99). Rates were 2.40 (1.71-3.09) and 2.65 (2.10-3.21)/100 PY in those who were and were not on ABC, respectively, at the index MI, and 2.90 (2.01-3.78) and 2.44 (1.95-2.93)/100 PY in those who were and were not currently receiving ABC, respectively, post-MI. No association was seen with recurrent MI and either cumulative exposure to ABC (RR=0.86 [0.68-1.10]/5 years), receipt of ABC at index MI (0.90 [0.63-1.29]) nor recent post-MI exposure to ABC (1.19 [0.82-1.71]). CONCLUSIONS: Among people with a previous MI, there was no evidence for an association between use of ABC post-MI and an elevated risk of a recurrent MI.

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Abacavir use and risk of recurrent myocardial infarction

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Objective: To investigate the association between abacavir (ABC) use and recurrent myocardial infarction (MI) among HIV-positive people with a prior MI.

Design: International multicohort collaboration with follow-up from 1999 to 2016.

Methods: The rate of recurrent MI was described among D:A:D participants who experienced an index MI whilst in the study, and who remained under follow-up beyond 28 days after this MI. Follow-up was considered to the date of next MI, death, 1 February 2016 or 6 months after last clinic visit. Poisson regression models considered associations between recurrent MI and exposure to ABC (use at index MI, current post-MI exposure and cumulative exposure), before and after adjusting for calendar year.

Results: The 984 individuals who experienced an index MI during the study (91.3% male, median age 51 at index MI) were followed for 5312 person-years, over which time there were 136 recurrent MIs (rate 2.56/100 person-years, 95% confidence interval 2.13–2.99). Rates were 2.40 (1.71–3.09) and 2.65 (2.10–3.21)/100 person-years in those who were and were not on ABC, respectively, at the index MI, and 2.90 (2.01–3.78) and 2.44 (1.95–2.93)/100 person-years in those who were and were not currently receiving ABC, respectively, post-MI. No association was seen with recurrent MI and either cumulative exposure to ABC [relative rate 0.86 (0.68–1.10)/5 years], receipt of ABC at index MI [0.90 (0.63–1.29)] nor recent post-MI exposure to ABC [1.19 (0.82–1.71)].

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Conclusion: Among people with a previous MI, there was no evidence for an association between use of ABC post-MI and an elevated risk of a recurrent MI.

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Introduction

Since the initial presentation of findings from the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study in early 2008 demonstrating a 90% increase in the risk of myocardial infarction (MI) in HIV-positive individuals receiving antiretroviral therapy (ART) regimens that included abacavir (ABC) [1], other studies have reported inconsistent findings [2–5]. A recent updated analysis from the D:A:D study, which included follow-up and events from 2008 onwards, reported that the relative rate (RR) for MI associated with recent ABC use in the post-2008 period was unchanged from that previously reported [6]. These findings, in the context of demonstrated changes in the characteristics of those receiving ABC-based regimens, suggested that the association was unlikely to be explained by a higher underlying risk of MI in ABC-treated individuals prior to starting the drug.

Most of the studies that have considered the association between ABC exposure and MI risk, including the D:A:D analyses, have focussed on populations of HIV-positive people in which few individuals have already experienced a prior MI. However, such individuals represent a very high-risk subgroup that will likely be exposed to multiple lifestyle and clinical interventions for secondary prevention. We investigated the association between ABC use and subsequent MI risk among the patients who had already experienced an MI during prospective D:A:D follow-up.

Methods

Study design

The D:A:D study was an observational study of more than 49 000 HIV-1-positive patients from 11 cohorts from Europe, Australia, and the United States [7]. The primary study aim was to investigate associations between the use of ART, and the risk of cardiovascular disease (CVD) and other major disease events. The standardized dataset, collected prospectively during routine clinic visits, includes information on sociodemographic factors, AIDS events and deaths, risk factors for CVD, laboratory markers for monitoring HIV (including $CD4^+$ cell count and HIV RNA) and CVD, ART and treatments that influence CVD risk.

Information on incident MI events was reported to the study co-ordinating centre via a study event form which captured detailed information about the event and related circumstances. Each reported event was validated and coded using criteria applied in the WHO Multinational mONItoring of trends and determinants in CArdiovascular (MONICA) disease study [8], with this process being performed blind to information about the patient's ART status. Reported MIs were classified as definite, possible or unclassifiable using standardized criteria for classification including relevant symptoms, relevant increase and decline in cardiac enzymes, ischemic changes in electrocardiographic readings and, in cases of death, autopsy results if available. Fatal MI events were additionally validated using information collected on the Coding of Causes of Death (CoDe) form [9], and all complex and/or fatal MI cases were additionally validated with the input of an independent cardiologist.

Statistical methods

We considered the rate of recurrent MI among D:A:D participants who experienced an MI during study follow-up (the 'index' MI) and who remained alive and under follow-up at 28 days post-MI (to exclude any index MIs resulting in death). Follow-up was considered from 28 days post-MI to the first date of next MI, death, 1 February 2016 or 6 months after last clinic visit. Sixty-four of the individuals (6.5%) had experienced an MI prior to D:A:D entry (and prior to the index MI); to be consistent with the main D:A:D analyses, we did not exclude this subgroup, but sensitivity analyses (which excluded the subgroup) suggested that our findings were robust to their inclusion.

Poisson regression models were used to evaluate associations between recurrent MI and exposure to ABC. As in previous analyses of the dataset [5], each individual's follow-up was split into a series of consecutive 1-month periods, and his/her clinical, immunologic and virologic status at the start of each period was established. Three different exposures to ABC were considered: use of ABC at the time of initial MI (time-fixed); current, post-MI exposure (time-updated, defined as currently receiving ABC or having received the drug at any time in the 6 months leading up to the start of each month) and cumulative exposure (time-updated, including exposure both pre and post-MI and scaled to reflect a 5-year increment). Fixed confounders considered were sex, ethnic group, and mode of HIV acquisition. Time-updated covariates considered were calendar year, age

(continuous covariate), smoking status, BMI, cumulative exposure to the protease inhibitors lopinavir, indinavir and darunavir, and the development of dyslipidaemia, diabetes mellitus or hypertension (Table 1).

All analyses were performed using SAS version 9.3.

Results

Of the 1191 participants who developed an index MI during the study, 984 remained under follow-up for at least 28 days and were included in the study. These individuals were largely male (91.3%) and infected with HIV through sex between men (58.8%). At the time of the index MI, the participants had a median age of 51 years [inter-quartile range (IQR) 45–59], the majority were current (55.5%) or ex-smokers (24.3%), 14.3% had a family history of MI, and most had either a moderate (10–20%, 33.0%) or high (>20%, 27.1%) 10-year predicted Framingham risk for CVD. The index MI had occurred in 1999 to 2001, 2002 to 2004, 2005 to 2007, 2008 to 2010, 2011 to 2013 and from 2014 to 2016 in 95 (9.7%), 209 (21.2%), 207 (21.0%), 196 (19.9%), 184 (18.7%) and 93 (9.5%) participants, respectively.

Table 1. Univariate associations between ABC exposure and established CVD risk factors and subsequent myocardial infarction.

Factor	RR (95% CI)	*P* value
Cumulative exposure to ABC (/5 years)	0.86 (0.68, 1.10)	0.23
On ABC at time of MI	0.90 (0.63, 1.29)	0.58
Recent use of ABC	1.19 (0.82, 1.71)	0.36
Calendar year (time-updated)		
1999–2001	7.73 (3.36, 17.79)	0.0001
2002–2004	3.28 (1.79, 6.02)	0.0001
2005–2007	2.25 (1.25, 4.04)	0.0001
2008–2010	1.54 (0.86, 2.76)	0.15
2011–2013	1.01 (0.55, 1.85)	0.97
2014–2016	1	–
Sex		
Male	0.85 (0.47, 1.54)	0.59
Female	1	–
Age (/5 years older)	1.01 (0.99, 1.03)	0.19
Smoking status		
Current	1.07 (0.59, 1.95)	0.82
Ex	1.25 (0.69, 2.29)	0.47
Never	1	–
Unknown	1.04 (0.42, 2.61)	0.93
Ethnic group		
White	1	–
Non-white	0.86 (0.62, 1.21)	0.40
Mode of acquisition		
MSM	1	–
IDU	0.66 (0.36, 1.20)	0.17
Heterosexual	1.03 (0.68, 1.56)	0.89
Other/unknown	2.25 (1.25, 4.04)	0.007
Dyslipidaemia[a]	0.68 (0.40, 1.16)	0.16
BMI		
<18	1.14 (0.50, 2.60)	0.76
>18, ≤26	1	–
>26, ≤30	0.90 (0.57, 1.44)	0.67
>30	1.01 (0.49, 2.09)	0.97
Not known	2.29 (1.19, 4.40)	0.01
Diabetes	1.70 (1.15, 2.51)	0.008
Hypertension[b]	0.74 (0.48, 1.16)	0.19
Cumulative exposure to lopinavir (/5 years)	0.84 (0.58, 1.21)	0.35
Cumulative exposure to indinavir (/5 years)	1.21 (0.81, 1.80)	0.35
Cumulative exposure to darunavir (/5 years)	0.61 (0.29, 1.29)	0.20

ABC, abacavir; CI, confidence interval; IDU, injection drug users; MI, myocardial infarction; RR, relative rate.
[a]Total cholesterol at least 6.2 mmol/l, HDL cholesterol 0.9 mmol/l or less, triglyceride at least 2.3 mmol/l or receipt of lipid-lowering medication.
[b]Systolic blood pressure above 140 mmHg, diastolic blood pressure above 90 mmHg or receipt of antihypertensive or angiotensin-converting enzyme inhibitor medication.

The median $CD4^+$ cell count at index MI was 511 (IQR 348–740) cells/μl. At the time of index MI, the majority of participants (959, 97.5%) had ever received ART, with 860 (87.4%) of patients currently receiving ART. Two-thirds (691, 70.3%) had an HIV RNA less than 50 copies/ml. Of the 584 people who were not already receiving lipid-lowering drugs at the time of the index MI, 306 (52.4%) started them within the first 28 days after MI. Similarly, 245/763 (32.1%) of those not already receiving angiotensin-converting enzyme inhibitors and 330/699 (47.2%) of those not already receiving antihypertensives started these within the first 28 days after index MI. Two-thirds of participants (63.2%) received an angioplasty and 44 (4.5%) received coronary artery bypass surgery in the first 28 days after MI.

In all, 503 (51.2%) people had received ABC prior to their index MI for a median of 3.1 years (range 0–13.9) of whom 327 were still on ABC at the time of the index MI. Two hundred and thirty-nine of the 327 (73.1%) stopped the drug at a median of 323 (range 0–5252) days after MI, with 71 of them subsequently re-starting the drug. Eighty of the 481 participants who had not previously received ABC prior to the index MI (16.6%) started the drug for the first time at a median of 1089 (range 3–4384) days after the index MI. Of the 151 people who either started ABC for the first time or who restarted ABC after previous use, the majority (116/151) did so prior to the publication of the initial D:A:D study findings in 2008 [1].

The 984 included participants were followed for a median of 4.7 (range 0.1–15.3) years after the index MI (total person-years 5312). Over this time, 136 people (13.8%) had at least one recurrent MI [rate 2.56/100 person-years, 95% confidence interval (CI) 2.13–2.99]. Rates of recurrent MI were 2.40 (1.71–3.09, 47 events over 1959 PY) and 2.65 (2.10–3.21, 89 events over 3353 PY)/100 PY in those who were and were not on ABC at the time of their index MI; rates were 2.90 (2.01–3.78, 41 events over 1415 PY) and 2.44 (1.95–2.93, 95 events over 3897 PY)/100 PY in those who were and were not currently receiving ABC post-MI, respectively. There was no significant association between recurrent MI and either cumulative exposure to ABC [RR 0.86 (0.68–1.10)/5

years], receipt of ABC at index MI [0.90 (0.63–1.29)] or current post-MI exposure [1.19 (0.82–1.71)] (Table 1). Whilst earlier calendar year, a non-sexual or injection drug use route of HIV acquisition and a prior diagnosis of diabetes were each associated with an increased risk of recurrent MI in univariate analyses (Table 1), adjustment for these factors did not reveal any significant associations with exposure to ABC.

Conclusion

Whilst previous study findings have suggested that current use of ABC in HIV-positive people is associated with an almost doubling in MI risk [1], we found no evidence that use of ABC was associated with an elevated risk of recurrent MI in those with a previous MI. Although most of the continued/new ABC use in those with an MI was in the earlier years of the study, when the risk of recurrent MI was higher than it is currently [10–12], adjustment for calendar year did not modify our findings.

Whilst these results appear to contradict with previous findings, there are two main reasons why we might expect the association with ABC exposure to differ in those with a prior MI. Firstly, recurrent MIs in those with an index MI are more likely to reflect the uptake and success of post-MI interventions to manage CVD and prevent subsequent cardiovascular events in this group than differences in established risk factors for a primary MI. Our finding that few of the established CVD risk factors are associated with recurrent MI, other than diabetes, supports the existence of a different set of risk factors for recurrent MI, a notion which is consistent with the limited literature from the general population [13–15]. Secondly, one of the reasons for the continued debate about the potential association between ABC and MI is that there is no confirmed biological mechanism for the association. Arguably, the most promising potential mechanism to date relates to the association reported between ABC and platelet reactivity [16–18], a mechanism that would be consistent with the apparent reversible nature of the ABC association with MI; a similar association has also recently been described with protease inhibitors [19]. We would, however, expect the majority of those with an MI to be receiving antiplatelet therapy, more recently with the dual combination of aspirin and clopidogrel, which could plausibly modify any effects of ABC on platelet reactivity. Unfortunately, we do not collect detailed information on the clinical presentation of each MI or on subsequent management and are therefore unable to assess the numbers treated in this way to test this hypothesis.

We note that our aim in the present study was to exclude the possibility that any of the established CVD risk factors may have confounded (and possibly obscured) an association with ABC rather than to identify risk factors for recurrent MI *per se*. For this reason, we have not investigated these established risk factors in more depth, or the potential role of chronic kidney disease, a factor previously demonstrated to be associated with CVD risk in the study [20]; information on the latter was often unavailable in the earlier years of the study, although, in more recent years, ABC may have been a treatment of choice in people with chronic kidney disease. Furthermore, we do not capture information on lifestyle/behavioural modifications, and so cannot investigate whether any changes in these may have modified the subsequent risk of recurrent MI and/or its association with continued or new ABC use. We cannot, therefore, rule out the possibility that our findings may result from residual confounding due to different post-MI management among those who are and are not receiving ABC.

In summary, among people with a previous MI, there was no evidence for an association between use of ABC post-MI and an elevated risk of a recurrent MI.

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Conflicts of interest

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